Remarks/Arguments

The Examiner has reopened prosecution. Claim 28 is canceled without prejudice. Claims 1, 2, 4-8, 10-16 and 18-27 are pending and under consideration.

Claim Rejections-35 U.S.C. §103 (Freund, Richards, Levin)

The Examiner has rejected claims 1, 2, 4, 5, 22-26 and 28 under 35 U.S.C. §103(a) as being unpatentable over Freund et al. (U.S. Pat. App. Pub. No. 2001/0008632) in view of Richards et al. (U.S. Patent Application Pub. No. 2003/0158176) and Levin et al. (The American Journal of Medicine, 1996, 100(1):S40-S48, Abstract only). The Examiner states that Freund teaches aqueous aerosols of anticholinergic agents including trospium chloride, ipratropium bromide and betamimetics including formoterol, salbutamol and fenoterol for inhalation in the treatment of respiratory passage diseases. The Examiner also states that Freund also teach an active agent concentration range of 10 mg/100 ml to 2000 mg/100 ml and a nebulizer delivering 12 ml of concentrate per operation which the Examiner has calculated to be between 1.2 mcg and 2400 mcg per operation. The Examiner asserts that the duration of trospium formulations are dose dependent and accordingly, the relationship of the dose of trospium is a characteristic of trospium. The Examiner concludes that Freund's teaching of a dose range which encompasses the instantly claimed dosage range means that the duration of action taught by Freund would be the same as that of the instant invention. Citing *In re Bes*t (195 USPQ 430) and *In re Fitzgerald* (205 USPQ 594) the Examiner argues that when the prior art discloses subject matter which there is a reason to believe that includes functions that are newly cited or identically the claimed invention, the burden is shifted to the applicants to prove that the subject matter shown in the prior art does not possess the characteristic relied on. The Examiner further states that there is no requirement that the person of ordinary skill would have recognized the inherent disclosure citing *Schering Corp. v. Geneva Pharm. Inc* ., 339 F.3d 1337, 1377, 67 USPQ2d 1664,1668 (Fed. Cir. 2003) and *Toro Co. v. Deere & Co*., 69 USPQ2d 1584, 1590 (Fed. Cir. 2004); but that the feature or result of the prior art embodiment is enough for inherent anticipation. The Examiner further cites *SmithKline Beecham Corp. v. Apotex Corp*, 403 F.3d 1331, 1343-

13-44, 74 USPQ2d 1398, 1407-07 (Fed. Cir. 2005) for the premise that a compound can be "inherently" anticipated in the prior art.

The Examiner further states that a reference that clearly names the claimed species anticipates the claim no matter how many other species are named. The Examiner asserts that the presently claimed trospium is disclosed by Freund in a short list of 4 anticholinergic agents and that formoterol is disclosed by Freund in a short list of 4 betamimetics.

The Examiner states that Levin teaches administration of an anticholinergic agent in combination with a B2 agonist by inhalation. The Examiner notes that Levin discloses that the combination produced a greater therapeutic effect than the agents administered separately. The Examiner notes that ipratropium is one of 4 anticholinergics disclosed by Freund and albuterol is one of 4 betamimetics disclosed by Freund.

The Examiner asserts that Richards teaches that anticholinergic (antimuscarinic) agents that include trospium are useful in treating COPD and asthma by inhalation or insufflation in the form of an aerosol or dry powder. The Examiner also states that Richards teaches that the dose depends on many factors including potency of the compound, the age and weight of the patient and the severity of the disease. The Examiner asserts that one of ordinary skill would have optimized the dose taught by Freund to maximize the therapeutic effects and minimize the deleterious effects of the active agent.

The Examiner then states that the skilled person would have found it obvious to combine the teachings of Freund, Levin and Richards to treat diseases such as COPD by inhalation of trospium because Freund teaches the usefulness of trospium and formoterol for treating respiratory passage disease and Richards teaches COPD and asthma as two respiratory diseases effectively treated by trospium and Levin teaches the usefulness of treating COPD by inhalation with a combination of an anticholinergic agent and a B2 agonist. The Examiner concludes that one would have been motivated to administer the active agents via inhalation to treat the respiratory system to minimize the amount of agent administered systemically thereby avoiding undesirable effects and to improve upon the known methods of treatment for COPD and asthma. The Examiner further concludes that one of ordinary skill in the art would have found it obvious to substitute

one known element (trospium) for another (ipratropium bromide). Applicants respectfully disagree.

The Examiner has made essentially the same rejection as was made in the previous Final Office Action except now Levin is added to the rejection. Applicants respectfully submit that the Examiner's position remains technically and legally incorrect.

Claim 1

The Examiner continues to insist that Freund "inherently" discloses the presently claimed "species" of the invention. This is simply not true. The Examiner must agree with this on some level given that the Examiner has not maintained the anticipation rejection over Freund. Applicants are not merely claiming trospium. Applicants are claiming a method of delivering a specific drug in a composition at a drug dosage range that provides a specific therapeutic effect. Freund does not disclose this "species". Freund discloses a list of drugs and a list of dosage ranges. In order to arrive at the presently claimed "species" based on Freund's disclosure, one must first pick from Freund's disclosure the specific drug, trospium, and then one must make a second choice regarding the specific dosage that result in 10 hours of therapy. Freund gives a generalized dosage range from 10 mg to 20,000 mg/100 ml for all 100 drugs. This dosage range is huge. Certainly one of skill in the art would not conclude from this range that all 100 drugs are effective across the entire range, or effective for 10 hours across the entire range, or that this range is equally applicable to each and every drug listed therein. Thus Freund has not disclosed the specific, presently claimed "species".

Furthermore, Applicants have shown (FIG. 1b) that the 10 hour duration of trospium is dose dependent; the Examiner agrees that this is so at the top of page 4 of the Office Action but argues that the claimed 10 hour therapy is inherent to the prior art because it is inherent to a dose of trospium. However, Freund does not disclose, suggest or recognize any such relationship between *any* dose and the duration of *any* effective therapy. Applicants are the first to correlate at least 10 hours duration of therapy of trospium with a specific dosage range of trospium. As discussed in *In re Antonie*, 195 USPQ 6 at 8, the parameter optimized in the fact pattern therein was not recognized by the prior art to be a result effective variable and the court concluded that there was no

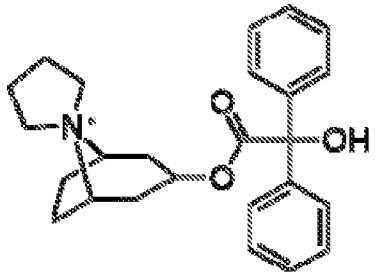
obviousness. Likewise, *In re Rijckaert,* 9 F.3d 1531, 1533 28 USPQ2d 1955 (Fed. Cir. 1993) the court states that in the absence of a disclosure or suggestion of the claimed relationship in the prior art, "that which may inherent is not necessarily known" and the Rijckaert court therefore concludes that "obviousness can not be predicated on what is unknown".

None of the cited references (Freund, Levin, Richards and Bernstein) recognize the relationship between the dose of trospium resulting in at least 10 hours of effective therapy. Freund is not about delivering anticholinergic agents and the treatment of related diseases. Freund is not about trying to make a long acting anticholinergic medicament. Freund does not teach or disclose the therapeutic effectiveness or hours of therapeutic effectiveness of any of the active ingredients listed therein. Freund's alleged discovery is that the spraying anomalies of aqueous pharmaceutical solutions for inhalation using a nebulizer can be reduced or minimized by the use of a complexing agent in the aqueous preparation. The therapeutic effectiveness of the solutions prepared by Freund was not tested. Only the ability of EDTA to minimize nebulizer anomalies in formulations containing drugs other than trospium is tested. The Examiner's analysis based on Freund relies on the person of skill in the art to *know* what the dose of any drug *should be* to achieve a desired therapy, to then calculate the amount required to be present in 12 microliters and then determine the concentration of the drug in the formulation. The Examiner has yet to provide any substantive arguments how a skilled person can know these things without the benefit of the present disclosure.

Levin does not provide what Freund or Richards lacks. Levin merely discloses that a specific anticholinergic that is *not* trospium, combined with a B2 agonist (albuterol) provides up to 8 hours of therapy. Levin notes that the effects of albuterol can be improved upon combination with ipratropium bromide. Levin does not disclose or suggest that there is a dose at which ipratropium *alone* can be effective for 10 hours or a dosage that provides a 10 hour effective therapy even when combined with albuterol. It should be noted that the last of Levin's data points are taken at 8 hours not 10 hours. Levin provides no information about trospium in general or the duration of trospium alone (claim 1) or the duration of trospium at any dose in combination with a B2 agonist (claims 22-28). The Examiner has provided no basis why the skilled person would

conclude that one anticholinergic agent such as trospium could be substituted with another such as ipratropium with any reasonable expectation of therapeutic effectiveness for at least 10 hours. It is well known that dose response, particularly duration of action, in drugs is dependent upon many factors including formulation, drug-drug interactions and the like. As evidenced by Bernstein, for example, the dose response such as duration of action are expected to be dependent upon other factors, in addition to the drug's properties, such as other components in the drug formulation or other drugs in the body that may enhance or diminish duration of action. It is noted that the Examiner concedes that such is the case in his characterization of Richards on page 6 of the Office Action.

As discussed in previous prosecution, trospium is not the compound formulated or tested in Richards. Richards merely mentions trospium as a known anticholinergic. Trospium is an anti-muscarinic and has the structure:



Richards discloses the synthesis and testing of novel anti-muscarinics that are very different from trospium. Richards simply teaches nothing about dosage or formulation or hours of therapeutic effectiveness of *trospium*. Anti-muscarinics belong to a functional class definition. Compounds that behave as anti-muscarinics are diverse structurally and functionally even with regard to their anti-muscarinic activity and potency. Thus the bronchodilatory effects of various dosages and formulations of trospium are not and cannot be disclosed in Richards. Given that the compounds in Richards are structurally different from trospium there is no basis for the Examiner's assumption that Richards provides any useful information with regard to the optimization of dosages and formulations of *trospium* which achieve effective therapy for at least 10 hours, either alone or in combination with Freund and, in fact, Richards acknowledges that the dose of anticholinergic agents depends upon many factors (page 6, paragraph 105 of Richards).

Therefore, as set forth in *In re Antonie* and *In re Rijckaert* in the absence of a disclosure, suggestion or recognition of the relationship between the dose of trospium and effective therapy of at least 10 hours, the Examiner has failed to establish that claim 1 is *prima facie* obviousness. Withdrawal of the rejection of this claim under this section is respectfully requested.

Claim 2

Claim 2 depends from claim 1 and recites that the disease to be treated is COPD. As Applicants have discussed in previous prosecution, it is simply not enough that the Examiner identify that others use antimuscarinic agents in the treatment of COPD. The Applicant's invention is the unexpected duration of therapy in the treatment of COPD using a *specific* antimuscarinic, trospium, not just any antimuscarinic. Richards and Levin each disclose and test an entirely different compound, the results of which have no bearing on the duration of therapy of specific formulations comprising trospium.

As discussed above with regard to Freund, Freund simply does not provide the skilled person with any guidance with regard to identifying a formulation of any drug that results in 10 hours duration of therapy. The claim limitation is simply not present in Freund either explicitly or inherently for the reasons discussed previously and the limitation is also not present in Levin or Richards. Therefore, the combination of Freund, Levin and Richards does not disclose or suggest all of the claim limitations of claims 1 and 2, for example.

Claim 4

Claim 4 depends from claim 1 and requires a specific dose of trospium. In addition to the discussion presented for claim 1, the combination of references does not make this claim obvious. While Freund generically provides a broad dosage range for the disclosed drugs (about 12 microliters at a concentration of 10 mg to 2000 mg drug per 100ml), and 200 to 800 micrograms (the claimed range) falls within the prior art range, this disclosure either alone or taken in combination with the other cited references does not support obviousness of claim 4. Richards teaches that the compounds described therein can be delivered to a human in an amount between 1 microgram and 1 mg [Para. 0108] which is outside the claimed range. Levin discloses that ipratropium is delivered at 500 micrograms in combination with albuterol which is within the claimed dosage

range, but does not show 10 hours of effective therapy of ipratropium delivered alone or in combination with albuterol, or of trospium delivered alone or with a beta-2-agonist.

Claim 5

Claim 5 depends from claim 1 and recites that the composition comprises an aqueous solution of trospium hydrochloride. For all the reasons discussed for claim 1, claim 5 is also not obvious over the cited combination of references.

Claim 22

Claims 22-26 include all of the limitations of claim 1. For the reasons discussed in detail above with respect to claim 1, claims 22-26 are not made obvious by the combination of Richards, Levin and Freund. There is no motivation provided by the references to combine *trospium* with any other active agent, such as beta-2 agonists or formoterol, while maintaining the claimed duration of therapy of trospium. In the discussion of claim 1, Applicants addressed the Examiner's assertion that it would have been obvious to simply substitute the ipratropium bromide of Levin with trospium or that 10 hours of effective therapy would be the result of such substitution. Such substitution would not be obvious nor expected to result in success. Withdrawal of the rejection of this claim under this section is respectfully requested.

Claim 23

Claim 23 depends from claim 22 and recites that the trospium is delivered with a beta-2 agonist. Neither Freund nor Richards disclose a species wherein trospium is delivered in combination with a beta-2 agonist. Levin discloses a *different* compound, ipratropium, delivered with a B2 agonist, albuterol. There is no basis for concluding that the skilled person would be motivated to combine trospium and a beta-2 agonist having the presently claimed duration of therapy. Therefore, claim 23 is not obvious over these references.

Claim 24

Claim 24 depends from claim 23 and recites that the trospium is delivered with formoterol. Freund does not disclose a species wherein trospium is delivered in combination with formoterol. While both trospium and formoterol are listed in the same 100+ drug list in Freund, there is no motivation provided by Levin or Richards for concluding that this very specific combination would be chosen out of the over 10,000

dual drug combinations theoretically described or that such combination will result in 10 hours duration of therapy. Therefore, claim 24 is not obvious over Freund, Levin and Richards.

Claim 25

Claim 25 depends from claim 23 and recites that the trospium and the beta-2 agonist are delivered separately. In addition to the discussion presented for claim 1, the combination of references does not make this claim obvious. The Examiner does not state where this limitation is found in Freund. Because Freund is not concerned with the actual treatment of a patient but is concerned with formulation stability, it does not teach this limitation and the rejection is clearly improper. Even Levin discloses that albuterol and ipratropium are delivered in the same formulation. Therefore, claim 25 is not obvious over Freund, Levin and Richards. Withdrawal of the rejection of this claim under this section is respectfully requested.

Claim 26

Claim 26 depends from claim 24 and recites that the trospium and formoterol are incorporated into the same formulation. While Levin does disclose that ipratropium and albuterol are delivered together in the same formulation, the Examiner has not provided any substantive reasoning as to why the skilled person would substitute trospium for ipratropium or that 10 hours of effective therapy can be achieved by selecting a dose of trospium that achieves the claimed duration of effective therapy. Therefore, claim 26 is not obvious over Freund, Levin and Richards. Withdrawal of the rejection of this claim under this section is respectfully requested.

Claim Rejections-35 U.S.C. §103 (Freund, Richards Bernstein and Levin)

The Examiner has rejected claims 1-2, 4-8, 10-16, and 18-28 under 35 U.S.C. §103(a) as unpatentable over Freund et al. (U.S. Pat. App. Pub. No. 2001/0008632) in view of Richards et al. (U.S. Patent Application Pub. No. 2003/0158176) as applied to claims 1, 2, 4, 5, 22-26 and 28 above, and further in view of Bernstein et al. (U.S. Patent Application Pub. No. 2004/0105821). From statements made in the Office action dated December 4, 2009, it appears that the Examiner also intended to include the reference by

Levin in the rejection. In an effort to be fully responsive Applicants are assuming that Levin is also included in the rejection and are addressing the rejection accordingly.

Freund and Richards are discussed above. The Examiner states that Bernstein teaches particulate sustained release pharmaceutical formulations for inhalation useful in treating asthma and COPD among others. The Examiner also notes that Bernstein teaches a sustained release formulation that provides local or plasma concentrations at nearly constant values of a period of up to 2 to 24 hours. The Examiner states that Bernstein teaches anticholinergic agents such as ipratropium bromide as bronchodilator agents but that Bernstein does not disclose or teach trospium *per se* but teaches anticholinergic agents in general. The Examiner further states that Freund also teach anticholinergic agents that can be administered by dry powder formulation as well as specifically teaching both ipratropium bromide and trospium. The Examiner concludes that one skilled in the art would have understood that one known anticholinergic agent could have been substituted with another with a reasonable expectation of success.

The Examiner notes that formulations disclosed by Bernstein utilize spray drying techniques and have aerodynamic diameters of the formulation that allow deposition in by inhalation in the region of interest in the lung. The Examiner further notes that Bernstein discloses other features of the particles that meet the limitations of present claims 8, 9, 11, and 12. The Examiner notes that Bernstein teaches the inclusion of surfactants and bulking agents including leucine in the formulations. The Examiner notes that Bernstein discloses that the active pharmaceutical agent is present from about 5 to 50% by weight and the Examiner presumes that the remainder of the formulation (i.e. between about 45-90 wt %) would be comprised of the bulking agent such as leucine.

The Examiner concludes that it would have been obvious to one of ordinary skill in the art to combine the 4 cited references to create an effective treatment for COPD and other respiratory diseases for inhalation to reduce undesirable systemic effects and to be long lasting to allow for once daily administration. The Examiner states that the reference to Levin teaches the therapeutic benefit of administration of an ipratropium and albuterol in the treatment of COPD. The Examiner states that Freund and Richards teach suitable therapeutic agents and routes of administration for treating COPD and Bernstein teaches methods for creating sustained release formulations for treating respiratory

diseases. The Examiner concludes that one would have been motivated to combine the treatments to improve upon the known methods of treatments for these diseases and the Examiner further asserts that the relationship of the dose of trospium to the duration of action is characteristic of trospium. Applicants respectfully disagree.

Claim 1

Freund does not teach or disclose the therapeutic effectiveness or hours of therapeutic effectiveness of the active ingredients listed therein. Freund's alleged discovery is that the spraying anomalies of aqueous pharmaceutical solutions for inhalation using a nebulizer can be reduced or minimized by the use of a complexing agent in the aqueous preparation. The therapeutic effectiveness of any of the solutions prepared by Freund is never tested. Only the ability of the complexing agent to minimize nebulizers with spray anomalies is tested with a formulation of ipratropium bromide and EDTA. Note that the other solutions of active ingredients listed in the table in paragraph 0051 are not even tested for nebulizer anomalies. Clearly one skilled in the art would not have "understood" that one anticholinergic agent such as trospium could be substituted with another such as ipratropium with any reasonable expectation of therapeutic effectiveness for any time frame based on Freund.

Likewise, Bernstein is directed to particle formulation and does not provide any evidence of the therapeutic effectiveness of any the hundreds of therapeutic agents listed therein (none of which are trospium). Only the physical characteristics of the particles prepared therein are tested in the Examples disclosed and then only the regional distribution of particles containing budesonide in the human lung is tested in Example 4. Bernstein provides no information or evidence with regard to the therapeutic effectiveness or hours of therapeutic effectiveness of the formulations or whether such formulations actually provide the extended release properties asserted in Bernstein. Further, Bernstein suggests that in order to provide a long acting formulation, one should encapsulate the drug into a sustained release matrix. The present inventors found this to not be necessary. With regard to the Examiner's presumption that between 45-90 % of Bernstein's formulation is bulking agent such as leucine (present claim 14), this amount of bulking agent is not a reasonable presumption in light of the disclosure of Bernstein. Instead Bernstein discloses in paragraph [0182] that the solid pore forming agent can be

between 10-100% (w/w) of the pharmaceutical agent and the matrix material. Note that none of the 6 formulations of budesonide containing microspheres exemplified in Bernstein (paragraphs 0196 and 0197) include any leucine at all. Therefore, the skilled person would not reasonably conclude that Bernstein is disclosing the presently claimed "at least 70% by weight of leucine" in any formulation. Bernstein does not make obvious the presently claimed leucine content for any particulate formulation disclosed therein.

With regard to Richards, Richards never tests *trospium* for therapeutic effectiveness over any period of time. As discussed above, Richards tests compounds having chemical structures that are entirely different from trospium. Therefore, the skilled person has no basis to conclude that an inhalable trospium formulation is capable of delivering 10 hours of effective therapy based on the cited combination of references.

In addition, Levin only discloses ipratropium in combination with albuterol and only tests the combination to 8 hours, not 10 hours as is presently claimed. Given the teachings of Richards and Bernstein regarding the many variables that can affect the dose of a particular compound, the skilled person would not assume that one cholinergic can simply be substituted for another cholinergic. None of the cited references disclose or suggest the presently claimed duration of therapy for any anticholinergic and none of the references disclose or suggest that trospium in particular can achieve the claimed duration of therapy at any dose. To establish a *prima facie* case of obviousness, the prior art reference (or references) when combined must teach or suggest all of the claim limitations (MPEP §2143).

Further, one of skill in the art would simply not combine Bernstein, Levin and Richards with Freund. Freund is directed to preventing spraying anomalies of a solution in a nebulizer. Bernstein is directed to making a dry powder for a dry powder inhaler or a suspension. Levin is directed to a particular combination of ipratropium and albuterol and Richards is directed to anticholinergic compounds that are not trospium. These are very different problems and the solution in Freund would not be applicable to the powders of Bernstein. One would look to Richards and conclude that the long acting compounds therein do not require the technology of Bernstein or Levin.

The Examiner has failed to establish a *prima facie* case of obviousness. Accordingly, withdrawal of the rejection of this claim under this section in view of the cited references is respectfully requested.

Claim 2

Claim 2 depends from claim 1. In addition to all the reasons discussed for claim 1, it is simply not enough that the Examiner identify that others use antimuscarinic agents in the treatment of COPD such as Richards and Levin. The Applicant's invention is the unexpected duration of therapy in the treatment of COPD using a *specific* antimuscarinic, trospium, not just any antimuscarinic. As discussed previously with regard to Freund, Freund does not provide the skilled person with any guidance with regard to identifying a formulation of any drug that results in 10 hours duration of therapy. The claim limitation is not present in Freund either explicitly or inherently for the reasons discussed previously and the limitation is also not present in Richards or Levin. Bernstein adds nothing to this discussion. Withdrawal of the rejection of this claim under this section is respectfully requested.

Claim 4

Claim 4 depends from claim 1 and recites a specific dosage if trospium. In addition to the reasons presented with regard to claim 1, the combination of references does not make claim 4 obvious. While Freund generically provides a broad dosage range for the disclosed drugs (about 12 microliters at a concentration of 10 mg to 2000 mg drug per 100ml), and 200 to 800 micrograms (the claimed range) falls within the prior art range, this disclosure either alone or taken in combination with the other cited references does not support obviousness of claim 4. Richards teaches that the compounds described therein can be delivered to a human in an amount between 1 microgram and 10 mg which is outside of the presently claimed range. Richards does not disclose or suggest that certain doses result in at least 10 hours of effective therapy. Levin discloses that ipratropium is delivered at 500 micrograms in combination with albuterol which is within the claimed dosage range, but does not show 10 hours of effective therapy of ipratropium delivered alone or in combination with albuterol. Bernstein adds nothing to the discussion. The claim is not obvious in view of the cited combination of references. Withdrawal of the rejection of this claim under this section is respectfully requested.

Claims 7 and 8

Claims 7 and 8 include all of the limitations of claim 1 and recite that the composition comprises a dry particulate formulation of trospium (claim 7) characterized by a fine particle fraction of at least 50% (claim 8) and wherein the formulation is administered with a dry powder inhaler. Fine particle fraction is defined on page 3, line 32 to page 4, line 2 as having an aerodynamic diameter of less than 3.4 microns as determined with an 8 stage cascade impactor. Freund, the primary reference does not disclose spray-dried formulations at all. Indeed, if one were to make a spray dried formulation for delivery by dry powder inhaler, one would not be concerned with Freund's spraying anomalies in the nebulizer. These are mutually exclusive technologies and problems and Bernstein, which is focused on spray drying, would not reasonably be combined with Freund. Levin also does not disclose spray dried formulations. Richards discloses powder formulations but does not disclose formulations of trospium.

In addition, none of the cited references discloses dry powder particles wherein the aerodynamic diameter of the actual particles in an 8 stage cascade impactor is actually measured, much less teach the fine particle fraction limitation. All of the dry particle formulations of trospium tested in the present application have an FPF of at least 50% and provided the greatest protection (greater than 20 hours) from bronchoconstriction even as compared to the aqueous composition of trospium tested (see page 15, lines 23-30 and Figure 3). Therefore, it is unexpected that the presently claimed dry powder formulations of claim 8 and all claims dependent thereon (claims 10-13, 15 and 18-21) would have the presently claimed duration of therapy. The cited combination of references does not disclose or suggest that duration of therapy or the claimed fine particle fraction of the trospium particle of claim 8 and all of its dependent claims. Withdrawal of the rejection of this claim under this section is respectfully requested.

Claim 10

Claim 10 depends on claim 8 and requires the trospium to be spray dried. While Bernstein generally says that a preferred method of making its sustained release microparticles is by spray drying, the specifics of spray drying a trospium formulation to achieve a sustained release formulation (which does not rely on the addition of a matrix material) is not taught. Further, for the reasons set forth above with respect to claim 8,

one would not combine these teachings of Bernstein with the teachings of Freund. As such, claim 10 is not obvious over this combination of references. Withdrawal of the rejection of this claim under this section is respectfully requested.

Claim 11

Claim 11 depends on claim 10 and limits the tap density of the formulation. While Bernstein teaches a single budesonide formulation with a tap density that falls within the scope of the claim, the rejection fails to explain why one would select this density and spray dry a trospium formulation. Further, the data suggests that increasing porosity decreases the long acting property over a 5.5 hour period (FIG. 1). This data does not support the allegation that a long acting formulation of trospium can be made in a light porous particle. Further, for the reasons set forth above with respect to claim 8, one would not combine these teachings of Bernstein with the teachings of Freund. As such, claim 11 is not obvious over this combination of references. Withdrawal of the rejection of this claim under this section is respectfully requested.

Claim 12

Claim 12 depends on claim 11 and requires the mass median aerodynamic diameter of the particles to be less than 5 microns. Bernstein simply does not teach, nor does it teach the desirability to combine, low porosity and small aerodynamic diameters with spray dried trospium to achieve long acting therapy. Clearly, Freund and Richards fail to teach these limitations as well. Further, for the reasons set forth above with respect to claim 8, one would not combine these teachings of Bernstein with the teachings of Freund. As such, claim 12 is not obvious over this combination of references. Withdrawal of the rejection of this claim under this section is respectfully requested.

Claim 13

Claim 13 depends on claim 12 and further requires the trospium to be spray dried with a phospholipid and/or leucine. While Bernstein generally says that a lipid, as well as many other materials, can be used in making the microparticles of the specification, he does not disclose the specific combination of trospium, phospholipid and/or leucine. Certainly, Freund does not suggest that his solutions can tolerate other divergent excipients. Further, for the reasons set forth above with respect to claim 8, one would not combine these teachings of Bernstein with the teachings of Freund. Richards is not

relevant either. As such, claim 13 is not obvious over this combination of references. Withdrawal of the rejection of this claim under this section is respectfully requested.

Claim 14

Bernstein does not disclose or suggest 70% leucine as asserted by the Examiner. As discussed above, Bernstein discloses very high percentages of solid pore forming agents and that is what is exemplified [paragraphs 182, 196, 197]. The teachings of Bernstein would not motivate the skilled person to make up the remainder of the particle with bulking agent only and certainly not as much as 70% bulking agent. The claim is not obvious in view of the cited combination of references. Withdrawal of the rejection of this claim under this section is respectfully requested.

Claim 15

Claim 15 depends on claim 14 and recites the relative amounts of trospium in addition to the leucine of claim 14 that provides a 10 hour duration of therapy as is shown in the Examples and Figures 1-3 of the specification. Claim 15 requires at least 70% leucine and less than 10% trospium. Nowhere in this rejection does it suggest that leucine is an excipient to be combined with trospium in this concentration. Bernstein does not teach or suggest the specific combination of trospium and leucine or the use of leucine at the presently claimed concentrations. Freund does not suggest that his solutions can tolerate other divergent excipients. Further, for the reasons set forth above with respect to claim 8, one would not combine these teachings of Bernstein with the teachings of Freund. Richards is not relevant either. As such, claim 15 is not obvious over this combination of references. Withdrawal of the rejection of this claim under this section is respectfully requested.

Claim 16

Claim 16 depends from claim 14 which ultimately depends from claim 1. In addition to the discussion presented for claim 1, the combination of references does not make this claim obvious. Claim 16 requires a specific dose of a specific formulation having about 5% trospium, 5-10% phospholipid and about 85-90% leucine. Nowhere in this rejection is this formulation suggested. Bernstein does not teach or suggest the specific combination or dose. Certainly, Freund does not suggest that his solutions can tolerate other divergent excipients. Further, for the reasons set forth above with respect to

claim 8, one would not combine these teachings of Bernstein with the teachings of Freund. Richards is not relevant either. As such, claim 18 is not obvious over this combination of references. Withdrawal of the rejection of this claim under this section is respectfully requested.

Claim 18

Claim 18 depends from claim 16 which ultimately depends from claim 1, and recites that trospium is administered at a dose of 200-800 mcg. For all the reasons discussed with regard to claim 4 above, claim 18 is not obvious over the cited combination of references. Withdrawal of the rejection of this claim under this section is respectfully requested.

Claims 19 and 20

Claims 19 and 20 also depend from claim 16 and ultimately from claim 1. In addition to all the reasons given for claim 1, claims 19 and 20 require a specific pharmacokinetic profile of a specific formulation having about 5% trospium, 5-10% phospholipid and about 85-90% leucine. Nowhere in this rejection is this formulation suggested, nor is the pharmacokinetic profile. Bernstein does not teach or suggest the specific combination or dose. Certainly, Freund does not suggest that his solutions can tolerate other divergent excipients. Further, for the reasons set forth above with respect to claim 8, one would not combine these teachings of Bernstein with the teachings of Freund. Richards is not relevant either. As such, claims 19 and 20 are not obvious over this combination of references. Withdrawal of the rejection of these claims under this section is respectfully requested.

Claim 21

Claim 21 depends on claim 8 and requires a method where the formulation is administered once a day. Given the fact that none of the references teach a formulation with a long acting therapy for trospium, the claim cannot be considered obvious. While Bernstein does teach once a day formulations, how to make a trospium once a day is simply not taught. The claim is not obvious in view of the cited combination of references. Withdrawal of the rejection of this claim under this section is respectfully requested.

Claims 22-26

Claims 22-26 include all of the limitations of claim 1. Likewise for the reasons discussed above with regard to the rejection over Freund, Levin and Richards, claims 22-26 are also not made obvious by the combination of Freund with Richards and Bernstein. As discussed above, Bernstein is no more relevant than Richards with regard to its teaching of combination therapies. There is no motivation provided by any of the references to seek a formulation of trospium, particularly one that provides 10 hours of therapy as discussed above, and there is no suggestion or motivation to combine trospium with any other active agent while maintaining the claimed duration of therapy of trospium. The cited combination of references does not disclose or suggest the claimed features of these claims. Withdrawal of the rejection of this claim under this section is respectfully requested.

Claim 27

Claim 27 includes all of the limitations of claims 1, 22, 23, 24 and 26 and recites that the composition further comprises a spray dried formulation of trospium, formoterol, leucine and optionally a phospholipid (compare also claims 7 and 13). Freund is directed to aqueous formulations and does not disclose spray dried formulations of any drugs and particularly a spray dried formulation of trospium in combination with formoterol, leucine and optionally a phospholipid. Richards and Bernstein discuss spray dried formulations of various drugs but neither discloses nor suggests a spray dried formulation of trospium, formoterol, leucine and optionally a phospholipid. The skilled person would not be motivated based on Freund to produce a spray dried formulation comprising trospium, formoterol and leucine and optionally a phospholipid having a 10 hour effective therapy with any expectation of success. Withdrawal of the rejection of claim 27 under this section is respectfully requested.

Obviousness Type Double Patenting Rejection

The Examiner provisionally rejects claims 8 and 9-16 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 63-69, 76-84, 92-94 and 96-98 of copending Application No. 10/392,333. The Examiner states that although the conflicting claims are not identical, they are not patentably distinct from

each other because both are drawn to similar dry powder compositions comprising trospium and the administration of the compositions by inhalation. Applicants respectfully disagree.

Independent Claim 63 of USSN 10/392,333 as pending is as follows:

Non-polymeric particles for pulmonary delivery of trospium via a dry powder inhaler, the particles consisting of:

a. trospium;

b. leucine, wherein leucine is present in the particles in an amount between 75 and 85% by weight,

c. optional buffer or salt; and

d. optional sugar

said particles having a tap density of less than about 0.4 g/cm^3.

Independent claim 78 recites methods of pulmonary delivery of the particles similar to those of claim 63. None of the claims disclose or suggest a dose or dose range of trospium. None of the reference claims disclose or suggest that there is a relationship between any dose of trospium and 10 hours of effective therapy. For all the reasons discussed previously in the context of *In re Antonie* and *In re Rijckaert*, in the absence of a disclosure of the relationship between the dose of trospium and 10 hours of effective therapy, the present invention is not obvious in view of the cited claims of USSN 10/392,333.

In addition, the claims of USSN 10/392,333 do not disclose or suggest treating diseases characterized by a constrictive airway. Claim 78 of USSN 10/392,333 only recites a method for pulmonary delivery of the claimed trospium composition; COPD or other respiratory diseases are *not recited* in the claims.

The Examiner has failed to establish that the present claims are obvious in view of the referenced claims of USSN 10/392,333. Withdrawal of the rejection under this section is respectfully requested.

Information Disclosure Statement

An Information Disclosure Statement is being filed concurrently herewith.

A general authorization is hereby granted to charge Deposit Account No. 502807 for any fees required under § 37 C.F.R. 1.16 and 1.17 in order to maintain pendency of this application.

Conclusion

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (978) 251-3509.

Respectfully submitted,

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